Development of a Stem Cell-based Transplantation Strategy for Treating Age-related Macular Degeneration

Grant Award Details

Development of a Stem Cell-based Transplantation Strategy for Treating Age-related Macular Degeneration

Grant Type: Early Translational I

Grant Number: TR1-01272

Project Objective: Develop a new treatment for age-related macular degeneration (AMD) based on transplantation of retinal pigment epithelial (RPE) cells into the subretinal space of a patient's eyes. The project planned to test stem cells from the CMZ of human eyes as well as iPSC. The project also planned to test the role of complement in the pathology of AMD by expressing complement inhibitors in transplanted RPE.

Investigator:

Name:	Gabriel Travis
Institution:	University of California, Los Angeles
Type:	PI

Disease Focus: Vision Loss

Human Stem Cell Use: Adult Stem Cell, iPS Cell

Award Value: $5,487,136

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Grant Application Details

Application Title: Development of a Stem Cell-based Transplantation Strategy for Treating Age-related Macular Degeneration

Public Abstract:

Age related macular degeneration (AMD) is a blinding disease of the elderly affecting nearly one in three individuals over the age of 75. Central vision is lost in AMD, severely impairing the ability to read, watch television, or drive. The epicenter of AMD is the retinal pigment epithelium (RPE), a single layer of cells in the retina adjacent to the photoreceptor cells. A recent breakthrough in AMD research showed that this disease is caused in about 50% of cases by the innate immune system (complement system) inappropriately attacking RPE cells. Specifically, AMD results when regulators of the complement system, which normally protect the RPE, are weakened by mutations. This sickens and later kills the RPE, causing secondary degeneration of photoreceptors in the central retina (macula).

The goal of this proposal is to develop a strategy for transplanting stem-cell derived RPE cells into the eyes of patients with AMD. In the past, transplantation of RPE cells from postmortem donors yielded encouraging initial therapeutic effects that subsequently failed due to immune rejection. Current stem-cell technology offers the opportunity to avoid this complication. We plan to generate functional RPE cells from stem cells of the ciliary margin zone (CMZ) in the eye, or pluripotent stem cells induced from skin fibroblasts (iPS cells) taken from the same AMD patient who will later receive the induced RPE cells as a transplant.

The study of inherited blindness has benefited greatly from mouse genetic models, where new potential therapies can be tested and developed. One aim of this proposal is to produce RPE cells from mouse and human CMZ- and iPS-cell precursors. To establish that these cells are functional, we will test for two hallmarks of a fully differentiated RPE: (i) the ability to convert vitamin A into visual chromophore for photoreceptor-opsin pigments, and (ii) the ability to phagocytose photoreceptor outer-segments. In a later aim we will transplant these induced RPE cells into the eyes of two genetic “knockout” mice that lack the ability to synthesize visual chromophore. We will test for rescue of the biochemical defects, and correction of the blindness in these mutant mice. In another experiment, we will add to the induced RPE cells a gene that protects from inappropriate complement activation. These cells will be transplanted into the eyes of two other knockout mouse-models of AMD that exhibit abnormal activation of the complement system. We will study these mice to establish correction of the immune defect. Finally, we will test the safety of CMZ- and iPS-derived RPE cells by transplanting them into immune-deficient mice to confirm no tumor formation. At the end of the grant period, we expect to have a new and well-tested stem-cell based transplantation strategy that will be ready for phase-one clinical trials in AMD patients.

Statement of Benefit to California:	This proposal is to develop a stem-cell based transplantation approach for treating age-related macular degeneration (AMD). AMD is a severe and common disease of the elderly that causes central blindness. The prevalence of AMD increases with advancing age. By 75 years, approximately one in three individuals have some degree of visual loss due to AMD. Thus AMD is significantly more prevalent than Alzheimer disease. Patients with AMD lose the ability to drive, read, watch TV, and recognize faces. With advancing visual impairment, AMD patients lose the ability to care for themselves and others. Thus, AMD imposes a large social and economic burden on our society. As the population in California ages, this burden is expected to increase. The stem-cell based transplantation strategy in this proposal offers the real potential of slowing or arresting the progression of blindness in AMD patients. This alone would represent an important benefit to the people of California. Further, the project would advance innovative technology in stem cell therapy. This technology has application to other neurodegenerative diseases. The project will train new stem-cell researchers in California. As the project enters the clinical phase, it will engage new scientists and physicians and attract funding by the federal government. Further, the opportunity to treat a hugely prevalent disease like AMD will undoubtedly attract biotechnology investment in California. This stem-cell based transplantation approach to treat a major disease like AMD is well-aligned with the broad mission of CIRM and the objectives of the Early Translational Research Award program.